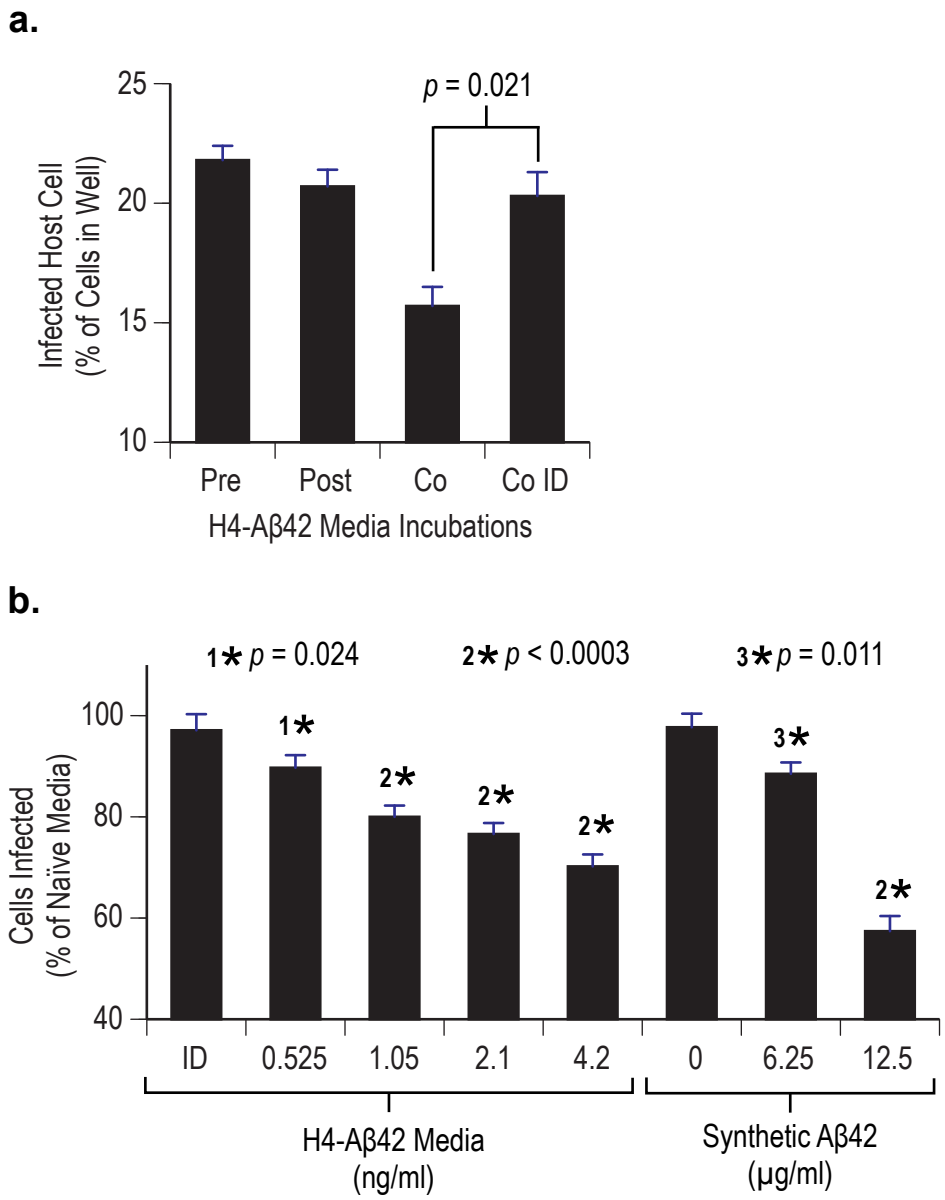
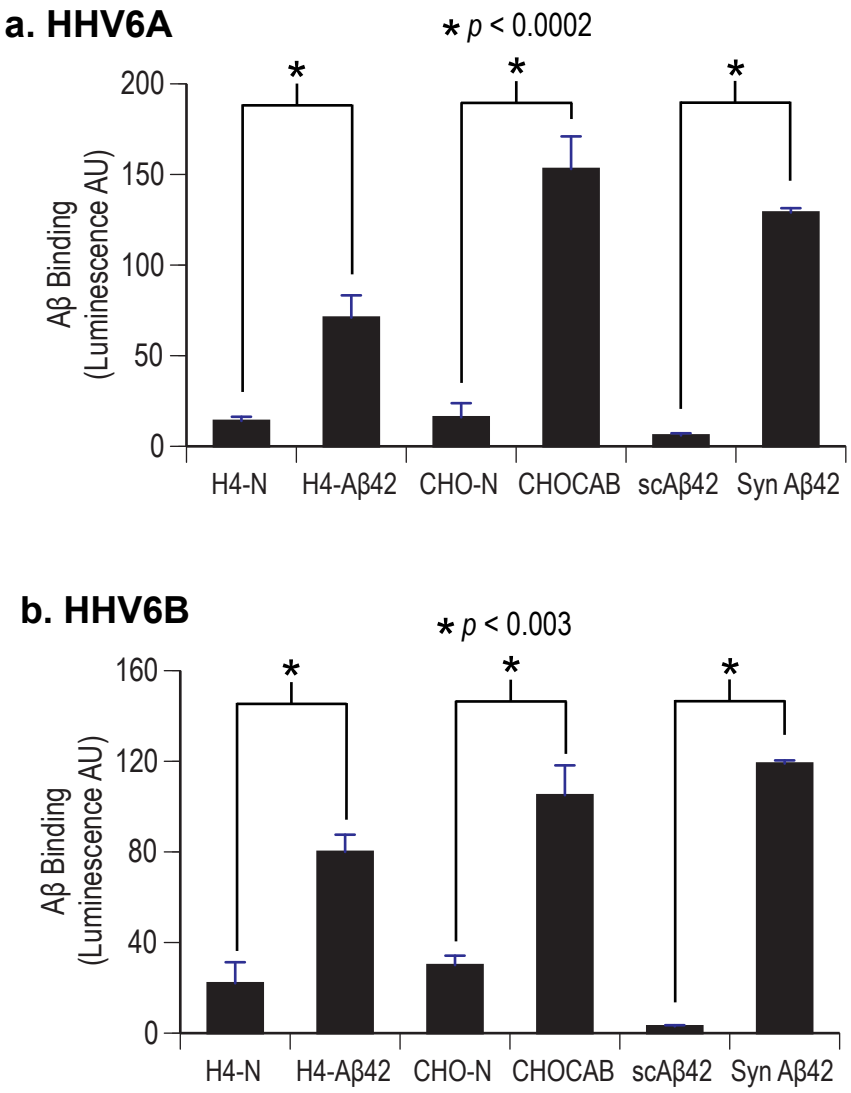
Sup. Fig. 1



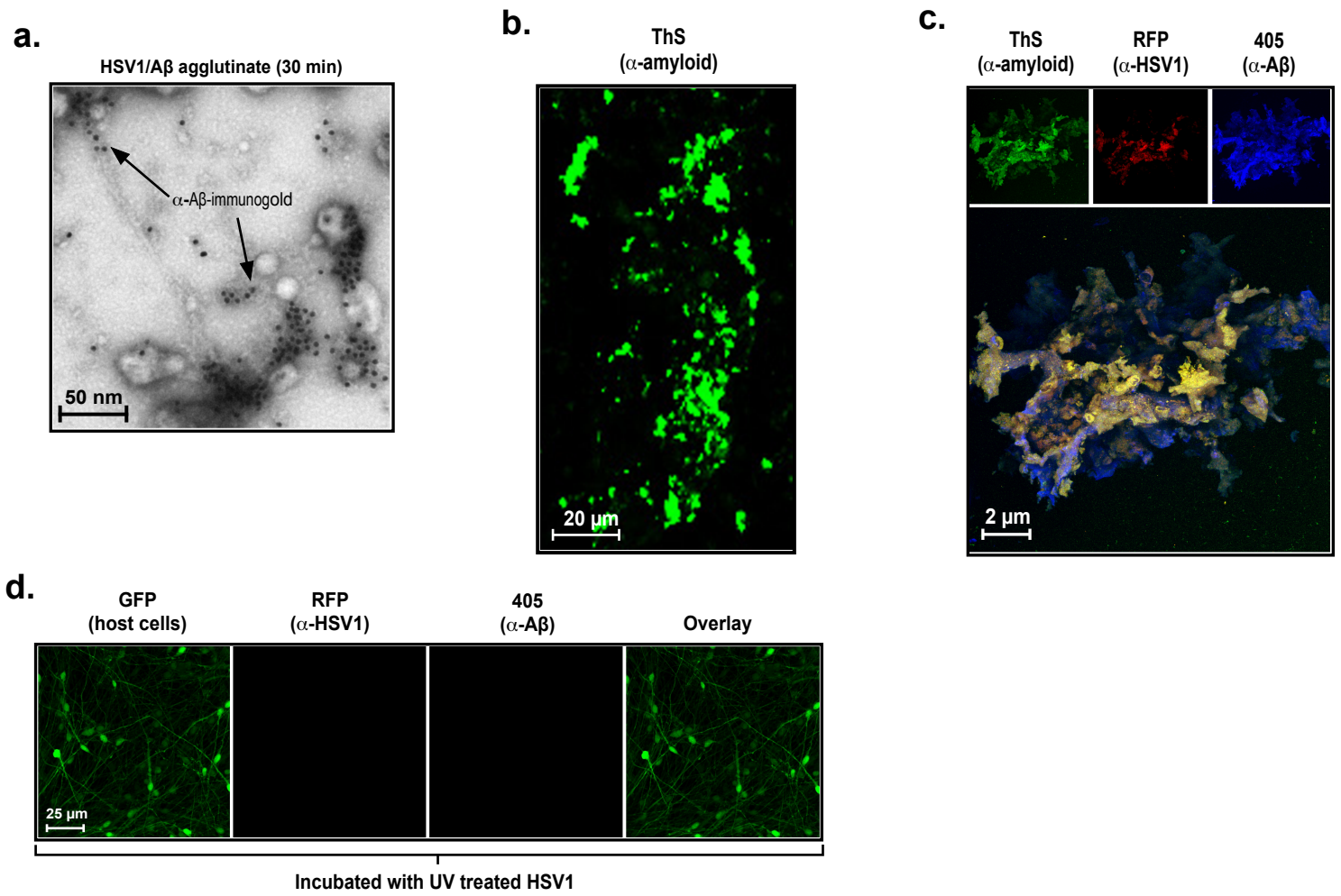
Supplemental Figure 1. ***Cell-derived Aβ oligomers directly bind and inhibit HSV1 particles in a concentration dependent manner.*** Virus binding was confirmed as mediating concentration-dependent antiherpetic activity of cell-derived oligomeric and synthetic monomeric Aβ42. Flow cytometry was used to measure host cell infection following incubation (2 hrs) of H4-N cell monolayers with HSV1-RFP. (**a**) Host cells were incubated with untreated or anti-Aβ immunodepleted (**ID**) H4-Aβ42 media before (**Pre**), following (**Post**), or with (**Co**) HSV1-RFP. Panel shows percentage of host cells with infection signal. Data are consistent with Aβ protection mediated by direct binding of HSV1. (**b**) H4-Aβ42 conditioned media or disaggregated synthetic Aβ42 were serially diluted using anti-Aβ immunodepleted (**ID**) media and sample Aβ concentrations determined by ELISA. Following co-incubation of samples and virus, host cells were assay for infection. Signal shown as percentage of positive control samples (naïve H4-N conditioned media). Data are consistent with concentration-dependent antiherpetic Aβ activity and potentiated (2-3 orders of magnitude) inhibitory activity for cell-derived oligomeric Aβ42 compared to monomeric synthetic. Bars show mean of replicate (n=6) wells ± SEM. Significance were calculated by t-test. Data is representative of at least 3 independent experiments.

Sup. Fig. 2



Supplemental Figure 2. ***Aβ binds HHV6A and HHV6B***. Aβ binding of HHV6 A and B was confirmed by herpes-binding ELISA. Wells containing heat-immobilized HHV6A or HHV6B were incubated (1 hr) with conditioned media from transformed Aβ overexpressing cells (**H4-Aβ42** and **CHO-CAB**), matching negative control naïve cell lines (**H4-N** and **CHO-N**), or synthetic Aβ42 (**Syn Aβ42**) or scrambled (**scAβ42**) peptides (12.5 µg/ml). Bound Aβ was then detected immunochemically. Consistent with finding for HSV1, data confirms binding of cell-derived Aβ oligomeric species to HHV6A and HHV6B at physiological peptide concentrations (2-4 ng/ml). Synthetic Aβ42 prepared under conditions that inhibit soluble oligomer generation bound HHV6 viruses at higher peptide concentration. Bars are mean signal of replicates (n=4) ± SEM. Statistical mean comparisons were done by *t*-test. Panels show data representative of finding from at least 3 independent experiments.

Sup. Fig. 3



Supplemental Figure 3. ***HSV1 seeds Aβ fibrillization in cell culture leading to virus capture and entrapment in β-amyloid.*** Aβ/HSV1 aggregates generated in cell culture were probed for co-localization of β-amyloid (**β-amyloid**) with Thioflavin S (**ThS**) and immunoprobed with anti-HSV1 (**α-HSV1**), anti-Aβ fluorophore (**α-Aβ**) or immunogold (**α-Aβ-immunogold**) labeled antibodies. Samples were analyzed for immunogold signal by TEM and green (**GFP**), red (**RFP**), and blue (**405**) fluorescence using confocal microscopy. (**a**) Following HSV1 incubation in H4-Aβ42 media insoluble aggregates were isolated and incubated with anti-Aβ immunogold. Consistent with identity as β-amyloid fibrils, immunogold particles labeled the fibrillar network entrapping HSV1 particles. (**b-c**) Cell-free matrigel containing H4-Aβ42 conditioned media was incubated (2 hrs) with HSV1, fixed, and probed. The human neuronal cells used in our 3D cell culture model express GFP. GFP fluorescence interferes with signal from Thioflavin S. Cell-free matrigel allowed confirmation that Aβ in HSV1 aggregates is fibrillar β-amyloid, consistent with findings for 5XFAD mouse brain (**Fig. 4e**). (**d**) Three-week old 3D human stem cell-derived transformed neural cell cultures were incubated (48 hrs) with UV-irradiated HSV1, sectioned, and probed. Findings confirm that without viral replication low HSV1 titers introduced to initiate infection are insufficient to generate readily detectable levels of β-amyloid. Data are consistent with new viruses generated following HSV1 host cell infection mediating the extensive β-amyloid deposition reported in **Fig. 4b-c**.